

DNA and RNA

Introduction

These antibiotics are not related to each other except that they inhibit DNA or RNA in some way. To do that, they must get into the bacterial cytoplasm. This lesson will feel a little like a hodge-podge, because it is. There will also be a theme of being used to treat urinary tract infections. Do not fall into that trap. That is NOT why they are taught together. They are categorized loosely by their mechanism of action's being related to DNA synthesis or RNA transcription.

The drug classes are fluoroquinolones which target topoisomerases, sulfonamides and trimethoprim which inhibit nucleic acid synthesis, and then some drugs that have an unknown mechanism but definitely screw up bacteria—nitrofurantoin and metronidazole. At a superficial level, nitrofurantoin and metronidazole have similar-sounding mechanisms; pay close attention to their differences.

CLASS/DRUG	MECHANISM	SIDE EFFECT	NOTES
Fluoroquinolones (ciprofloxacin)	Topoisomerase 2 inhibition	Tendon rupture	100% oral bioavailability Treats Gram negatives Used in gut infections
Fluoroquinolones (moxifloxacin)	Topoisomerase 4 inhibition	Tendon rupture	Gram positive (strep) Used in CAP
Sulfonamides (Sulfamethoxazole)	Inhibit bacterial synthesis of di-hydro-folate	Renal failure Sulfa allergies Kernicterus (neonates) Displace albumin G6PD deficiency anemia Hemolysis	Never monotherapy, always as TMP/SMX
Trimethoprim	Inhibits all synthesis of tetra-hydro-folate	Megaloblastic anemia	Never monotherapy, always as TMP/SMX PCP ppx CD4 < 200 PCP tx intravenous
Nitrofurantoin	Activated to highly active intermediates by bacteria, ruins DNA, RNA, proteins	N/A	3 g q3d for UTIs, never the first-line treatment
Metronidazole	No one knows, but it dun messed up all the things and dem bacteria DIE	Disulfiram reaction	Kills anaerobes, use with ciprofloxacin for gut infx Kills vaginal bacterial infections Kills fungus

Table 5.1: The Drugs in This Lesson, Summarized

Fluoroquinolones

The bacterial form of topoisomerase 2, bacterial **DNA gyrase**, normally acts to alleviate the tension on the double-stranded DNA caused by DNA helicase during replication. The supercoiled DNA is under significant stress, and would break if not for the action of DNA gyrase. Fluoroquinolones **inhibit bacterial DNA gyrase**, resulting in stressed DNA's breaking. Breaking DNA means the cell dies, so these are **bactericidal**. Fluoroquinolones also inhibit topoisomerase 4, which provides stability of DNA during mitosis.

Fluoroquinolones are not interchangeable. The bactericidal effect of **inhibiting topoisomerase 2** carries more impact on Gram-**negative** organisms than on Gram-positive. In direct opposition, the bactericidal effect of **inhibiting topoisomerase 4** is more important in Gram-**positive** organisms (like strep) than in Gram negatives. Therefore, the fluoroquinolone with a higher affinity for topoisomerase 4 will be used against Gram-positive organisms, while the fluoroquinolone with a higher affinity for topoisomerase 2 should be used for Gram-negative organisms. This is why "**ciprofloxacin is a urinary fluoroquinolone**" (low topo 4 activity, high topo 2 activity), while "**moxifloxacin is a respiratory fluoroquinolone**" (high topo 4 activity, low topo 2 activity).

Ciprofloxacin is used to treat Gram-negative infections. It was the antibiotic of choice to cover ambulatory pyelonephritis. However, **growing fluoroquinolone resistance** has taken ciprofloxacin out of the rotation for UTIs. Ciprofloxacin has two main uses—empiric coverage for gut infections and as double coverage for *Pseudomonas* pneumonia. When combined with metronidazole (anaerobes), ciprofloxacin is good empiric antibiotic coverage for gut infections such as diverticulitis or appendicitis. When starting a patient on an antipseudomonal agent for a nosocomial pneumonia, ciprofloxacin should be added as a second antipseudomonal agent. Ciprofloxacin is never used as monotherapy for pneumonia, pseudomonal or otherwise. The only time you should think of using ciprofloxacin as monotherapy for any diagnosis is in treating *Pseudomonas* with drops—eye drops and ear drops. Ciprofloxacin has **100% bioavailability**—the oral dose has the same effect on plasma concentrations as the intravenous dose.

Levofloxacin can treat *Strep. pneumoniae*, and is older, cheaper, and better tolerated than moxifloxacin. For nonsevere pulmonary infections, levofloxacin is the go-to. When treating an ambulatory pneumonia or bronchitis, the options are azithromycin or doxycycline, and sometimes people use levofloxacin. You will see levofloxacin used in clinical practice to treat pulmonary infections. This is out of habit.

Moxifloxacin can treat ***Strep. pneumoniae* AND anaerobes**. It has a high affinity for topoisomerase 4, and little affinity for topoisomerase 2, which is why it has little effect on Gram negatives and good effect on *Strep. pneumo*. It is used to treat **community-acquired pneumonia**, often out of convenience, having both an oral and an intravenous form. CAP is the approved indication for moxifloxacin, even though we are coaching you to NOT use it that way. Overuse of fluoroquinolones has spread fluoroquinolone resistance. We did it with ciprofloxacin and UTIs and now we're doing it again with moxifloxacin and pneumonia. Convenience breeds resistance. The appropriate empiric antibiotic therapy for community-acquired pneumonia is ceftriaxone and azithromycin. For patients with **allergies to cephalosporins or macrolides**, moxifloxacin remains the alternate choice for community-acquired pneumonia. It does not concentrate in the urine, so is an ineffective antibiotic for UTIs. It has no effect on *Pseudomonas* in any of its forms, as compared to ciprofloxacin, which does.

CIPROFLOXACIN	LEVOFLOXACIN	MOXIFLOXACIN
High affinity topo 2; use for <i>Pseudomonas</i> (not monotherapy) Double cover for HAP	Not really relevant	Low affinity topo 2; do not use for <i>Pseudomonas</i>
Low affinity topo 4; do not use for <i>Strep. pneumoniae</i>	Not really relevant	High affinity topo 4; do use for <i>Strep. pneumoniae</i> CAP with cephalosporin allergy

Table 5.2: Fluoroquinolone Comparison

Side Effects. **Photosensitivity** makes patients on these medications highly susceptible to sunburns. In the **elderly** there has been **tendinitis** and **tendon rupture**. They must be avoided in children **under 18 years old** and in **pregnant women** because in animal models they have been shown to disrupt cartilage and cause arthropathy. The old people get tendon rupture; the babies get bad joints.

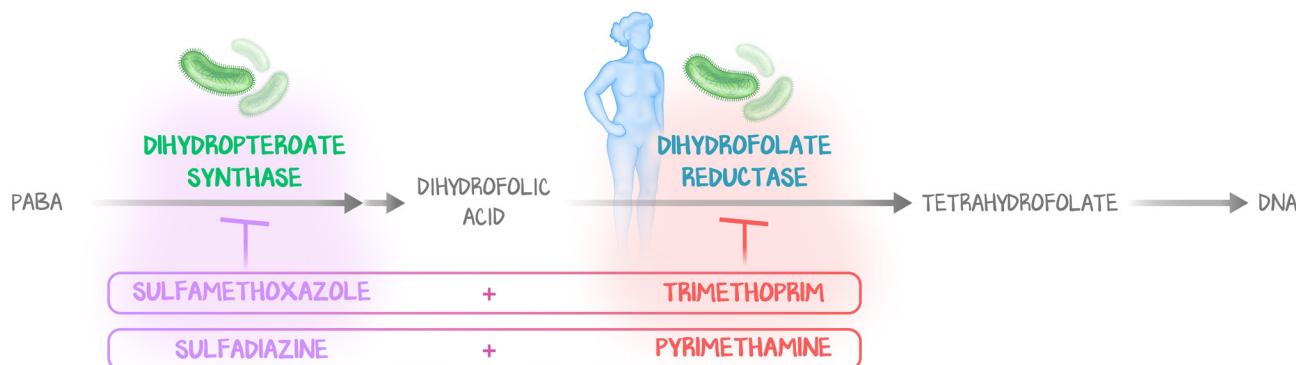
The FDA is literally begging people to stop using fluoroquinolones unless no alternative exists, especially for mild infections. As with vancomycin and MRSA, the overuse of ciprofloxacin for ambulatory UTIs diagnosed and prescribed over the phone (ciprofloxacin was never intended to be used for uncomplicated cystitis) and moxifloxacin for non-pneumonia respiratory symptoms (and sometimes wildly inappropriately used for viral respiratory infections), have bred fluoroquinolone resistance.

Inhibitors of Nucleic Acid Synthesis

Folic acid is an essential vitamin for a human—we cannot synthesize it. Folate is integral for the formation of **nucleic acids**. Humans must **eat folate** to make nucleic acids. Bacteria **synthesize folate** to make nucleic acids. Bacteria do this by combining two molecules (pteridine and PABA) via the enzyme **dihydropteroate synthetase**. Which makes di-hydro-pterid acid. This combines with glutamate to make **di-hydro-folate** (DHF). The final thing, the form of folate that is required to make nucleic acids, is called **tetra-hydro-folate** (THF). DHF is turned into THF by **DHF-reductase**. Only bacteria have dihydro-pterote synthetase. Both bacteria and humans have DHF-reductase.

There are two targets we can attack in the formation of tetrahydrofolate—the bacterial-only dihydropteroate synthetase that makes dihydrofolate, and the bacteria-and-human dihydrofolate reductase that makes the final tetrahydrofolate. It would be nice if we could actually go after the bacteria-only enzyme, but it doesn't work that way. Never use the dihydropteroate synthase inhibitors alone, as this simply breeds antibiotic resistance. There is synergy, however, in combining the dihydropteroate synthase inhibitors with dihydrofolate reductase inhibitors. O. M. G. is that a mouthful.

Laser focus and simplification. **Sulfamethoxazole** inhibits the first enzyme, **dihydropteroate synthase**, and is of the class sulfonamides. **Trimethoprim** inhibits the second enzyme, **dihydrofolate reductase**, and is of the class dihydrofolate reductase inhibitors. They are used only in combination to make Trimethoprim/Sulfamethoxazole, shortened to TMP/SMX. TMP/SMX is indicated for **prostatitis**, the intravenous treatment of *Pneumocystis jirovecii* (previously *Pneumocystis carinii* Pneumonia), known as "Pneumocystis Pneumonia," (PCP), and as **PCP prophylaxis in AIDS** patients with CD4 counts less than 200. PCP is now the colloquial term for *Pneumocystis something-or-other*, regardless of whether it is pneumonia or not, and the colloquial PCP term stuck even after the species got a new name. Call it PCP, you'll be happier if you do. TMP/SMX can even be used to treat MRSA cellulitis (though it is not first-line) and urinary tract infections (though it is most definitely not first-line). This hodge-podge of indications makes it hard to memorize, and its mechanism of action doesn't help solidify why it works. Which makes it great board fodder.

**Figure 5.1: Folate Pathway**

Sulfonamides block the enzyme only in bacteria, di-hydro-terri-ate (dihydropteroate) synthase. Dihydrofolate reductase inhibitors such as trimethoprim and pyrimethamine target the enzyme used by both humans and bacteria, di-hydro-folate reductase. Always use a sulfonamide in combination with a dihydrofolate reductase inhibitor.

Because you never give either TMP or SMX alone, we are teaching this drug, TMP/SMX, as though it is a common single drug, and the only example of the drug classes. There are others, but we want you seeing TMP/SMX as one drug to treat PCP, and the other drugs in the class, for very different purposes, and therefore as completely different drugs.

TMP/SMX can cause **bone marrow suppression** (in particular a megaloblastic anemia, though it can progress to a pancytopenia) because of the **trimethoprim** part. It is this side effect that you should be able to link to the mechanism of action—trimethoprim inhibits dihydrofolate reductase in both humans and bacteria, which inhibits the synthesis of THF. Without THF, the cells that are mitotically active (i.e., need nucleic acid to synthesize DNA) suffer the most. This can be alleviated by feeding folate to the human. TMP/SMX can cause **sulfa allergies** because of the **sulfonamide** part. The sulfonamide part can cause also cause a host of side effects: renal failure (acute interstitial nephritis), kernicterus in infants, displacement of drugs from albumin (warfarin toxicity), and, in **G6PD deficiency**, can cause hemolytic anemia. Ugh . . . how to remember this all? See the takeaway.

There is one other combination you should learn. The protozoal infection *Toxoplasma gondii* in the immunocompromised AIDS patient with ring-enhancing lesions in their brain is treated with **sulfadiazine + pyrimethamine**. But learn it as “toxo treatment” and not as “another example of sulfonamides paired with dihydrofolate reductase inhibitor.”

Takeaway: Trimethoprim/sulfamethoxazole treats PCP in AIDS patients; sulfadiazine + pyrimethamine treats toxo in AIDS patients. TMP/SMX causes bone marrow suppression and renal failure, and can't be used in G6PD-deficiency.

SULFONAMIDE	DIHYDROFOLATE REDUCTASE-i	COMBO USED FOR
Sulfamethoxazole	Trimethoprim	PCP in AIDS
Sulfadiazine	Pyrimethamine	Toxo in AIDS

Table 5.3: Real Medications in This Section are Combinations

Nitrofurantoin

Nitrofurantoin enters a bacterium, where it encounters **nitrofuran reductase**. This converts nitrofurantoin into highly active intermediates which cause inhibition of **pyruvate metabolism**, of **DNA replication**, and of **protein translation**. It is used in **urinary tract infections** when **amoxicillin** is unavailable or there is a penicillin allergy. It is safe in pregnancy, though amoxicillin remains the preferred agent. It is a commonly prescribed urinary tract infection antibiotic, but it rarely appears on board examinations because it is not well understood beyond “highly interactive intermediate, causes bacteria to get messed up.” You are likely to see it more in the clinical years.

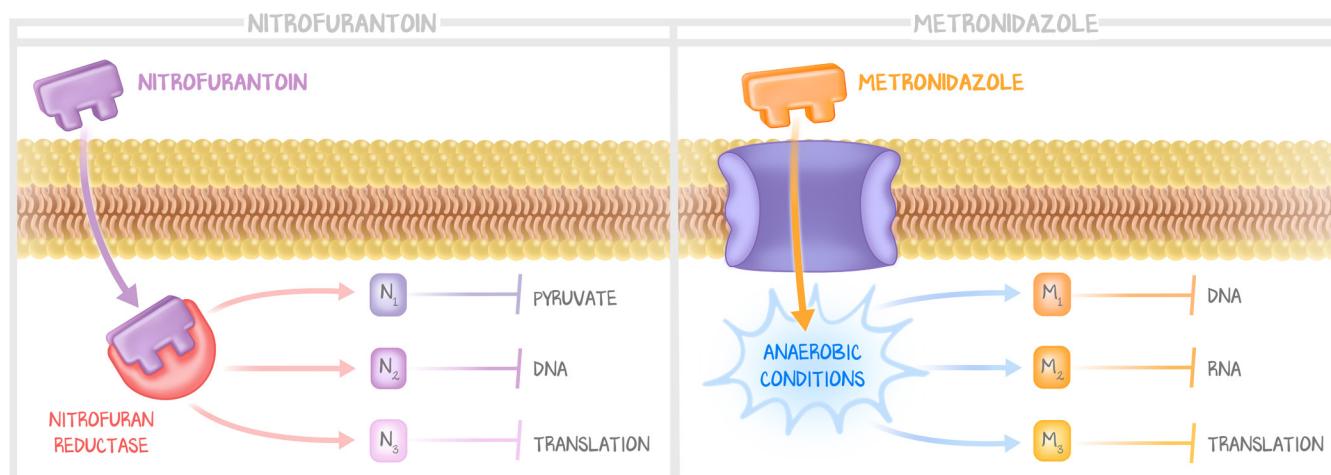


Figure 5.2: Nitrofurantoin and Metronidazole

Nitrofurantoin's mechanism of action is poorly understood. It gets into the cell somehow and is activated to highly active metabolites that inhibit pyruvate metabolism, transcription, and translation. Metronidazole's mechanism of action is also poorly understood. In anaerobic conditions it is activated to highly active intermediates which interfere with transcription and translation.

Metronidazole

Metronidazole has an unknown mechanism. We do know that it has a fairly broad range of effects. Here, we are discussing its **antibacterial effects**, even though it can also be used to treat parasites and fungus. It is included here because the mechanism is similar to that of nitrofurantoin. Metronidazole gets into the cell (we don't know how) and through an unknown mechanism (we don't know what it is), **under ANaerobic conditions**, it is transformed into **highly active intermediates** which cause inhibition of transcription and translation.

Metronidazole works in anaerobic conditions. In the first lesson we portrayed anaerobic coverage to be a choice between clindamycin and metronidazole. Metronidazole is used as empiric anaerobic coverage for infections of the abdomen, pelvis, and vagina, paired with coverage for Gram-negative organisms. For example, the combination of ciprofloxacin and metronidazole is empiric coverage for gut infections, as is ampicillin/gentamycin and metronidazole. Metronidazole is really good at killing anaerobes, is low cost, and well tolerated. Metronidazole should be used for **gut infection empiric coverage**. Out of convenience, pip/tazo has been used to treat gut infections, as it does cover Gram negatives and anaerobes. One antibiotic is easier to remember, order, and administer. But for sake of antibiotic stewardship, remember that using pip/tazo for gut infections covers *Pseudomonas* and strep species that do not need to be covered, erroneously exposing bacteria to an extended-spectrum β -lactam. Stop using pip/tazo for every infection! And build a repertoire of empiric coverage combinations for common infections.

Oral metronidazole WAS used for mild to moderate *C. diff* colitis. It WAS the first-line agent. *C. diff* is an anaerobic bacterium that causes disease of the GI tract, in the abdomen. It makes sense that metronidazole would be used to treat *C. diff*. Empiric data has proven that oral vancomycin, which is not absorbed, is more effective at treating *C. diff* colitis. Vancomycin we teach to be anti-staph only. This unexpected success of vancomycin and the obvious inferiority of metronidazole make the subject of *C. Diff* colitis treatment a key target for board examinations. Which is appropriate because this is a common infection in hospitalized patients. **Intravenous metronidazole** with oral vancomycin remains the treatment for severe *C. diff* colitis—the metronidazole attacking the *C. diff* from the bloodstream while the vancomycin attacks the *C. diff* from the lumen.

Metronidazole treats bacterial, fungal, and protozoal **vaginal infections**. Ingesting **alcohol while on metronidazole** causes a **disulfiram-like reaction** and the patient will **vomit violently**.